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Although experimental data suggest that ginseng has immunostimulating and cancer inhibitory properties, its effect and safety have not been adequately evaluated among breast cancer survivors. Soy has also been shown in laboratory studies to have anti-estrogenic and anti-cancer effects but epidemiologic data on soy and breast cancer recurrence is sparse. Limited data are available on the effectiveness and safety of other botanic and "natural" remedies that are marketed as anti-cancer agents. Potential beneficial or harmful pharmacological interactions of ginseng, soy, and other complementary medicines with conventional cancer therapies have not been well studied.

Funded by the DOD, we are conducting a large cohort study in Shanghai, China, to test the following hypotheses: 1) Ginseng use and high soy intake reduce breast cancer recurrence and improve overall survival; 2) Ginseng use increases quality of life among breast cancer survivors. We will also evaluate the potential effect of Chinese traditional medicine and other herbal or "natural" remedies on survival, recurrence, and quality of life. Interactions with conventional cancer therapies will be examined.

The study is progressing as planed. To date, 1981 breast cancer survivors have been recruited with an overall participation rate of 80%. The 18-month follow-up survey has been completed for 634 cases. No adverse events have been reported during the study period.

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Introduction

Breast cancer is the most common malignancy among U.S. women, with approximately 180,000 U.S. women being diagnosed with breast cancer each year. Attributed to advances in early diagnosis and treatment, 85% of breast cancer patients are expected to survive more than five years. However, survival does not mean one is cured. Many breast cancer survivors are constantly battling with the risk and fear of disease recurrence, pre-mature menopause and associated menopausal symptoms, lymphedema, fatigue, depression, and other post-trauma syndromes (1-3). Coping with and treating the physical and psychological consequences related to cancer survival and cancer therapies will not only affect the survival and quality of life of this rapidly expanding breast cancer survivor population, but also influence the medical care system and economy of society at large.

Using botanic remedies or other "natural" substances to assist recovery, treat post-treatment symptoms, and prolong life has become increasingly popular among breast cancer survivors (4-8). It has been reported that 8-37% of breast cancer patients in the U.S. have used botanic remedies after diagnosis of breast cancer at some point (5-8). The effectiveness and safety of most botanic remedies that are currently available on market, however, have not been systematically evaluated in human studies. Potential harmful pharmacological interactions between botanic remedies and conventional medicines have not been studied.

Ginseng, the third top-selling herb in the U.S. market, has been used to proactively promote health, vitality, and longevity in Asian countries for more than 2000 years. Cumulative data, mainly from *in vitro* studies, have suggested that ginseng has immunostimulatory and anti-carcinogenic properties. The effect of ginseng in improving breast cancer survival and quality of life, however, has not been systematically evaluated. Soy and its constituents have been shown in many *in vivo* and *in vitro* studies and in some epidemiological studies to have anti-cancer effects. Some soy constituents, however, also stimulate cell proliferation, and this property has raised some concerns regarding promoting soy intake among breast cancer survivors. Limited human data are available on the effectiveness of other natural remedies that are marketed as anti-cancer agents, such as fish oil and shark cartilage. Using traditional Chinese medicines, and certain unique exercises, such as Tai Ji and Qi Gong, in assisting disease recovery and prolonging the life of breast cancer patients also have historical roots, but have not been adequately evaluated in epidemiological studies.

Funded by the DOD Breast Cancer Research Program, we are conducting a cohort study of 2,250 women with newly-diagnosed breast cancer in Shanghai China. The major objective of the study is to systematically evaluate the effect of ginseng, soyfood intake, traditional Chinese medicines, and other complementary medicine use and their interaction with conventional cancer therapies on breast cancer survival, recurrence, and quality of life.

Study Design, Hypothesis, and Work Accomplished

This is a population-based cohort study. Through the population-based Shanghai Cancer Registry, women who are newly-diagnosed with invasive breast cancer after March 1, 2002 and who are between the ages of 20 and 74 at time of diagnosis are being recruited into the study. In-person and telephone interviews are conducted at 6, 18, and 36 months after diagnosis to collect information on the use of ginseng, soy, Chinese traditional medicines, and other complementary medicines. Quality of life is assessed and information on clinical symptoms at 6 and 36 months years after cancer diagnosis are collected by in-person interview. Information on cancer diagnosis and conventional treatment, breast cancer recurrence, and causes of death are verified through medical chart reviews. Tumor tissues are collected for testing estrogen and progesterone receptor status and for future study of markers of breast cancer prognosis. Second primary cancers and deaths are being identified through interviews and through record linkage to the Shanghai Cancer Registry database and Shanghai Vital Statistical Registry files. The effect of ginseng use, soyfood intake, and other complementary medicine use and their effect with conventional treatments on survival, recurrence, and quality of life will be evaluated, using appropriate statistical methods and controlling for known prognostic factors.

Specific hypotheses to be tested in the study are: 1) Ginseng use and high soy intake reduce breast cancer recurrence and improve overall survival and disease-free survival; 2) Ginseng use increases energy, reduces fatigue, and enhances overall quality of life among breast cancer survivors. We will also evaluate the potential effect of Chinese traditional medicine and other herbal or "natural" remedies (e.g., fish oil, shark cartilage) on survival, breast cancer recurrence, and quality of life. Interaction between the use of ginseng, soy, and other complementary medicines and conventional cancer therapies will be examined.

The first 28 months of the study was devoted to completing Task 1 of the proposal, as described below.

Task 1. Recruit 2250 newly-diagnosed breast cancer patients and conduct in-person and telephone interviews to collect information on complementary medicine use and quality of life, and to conduct medical chart review to verify information on cancer diagnosis, conventional treatments, breast cancer recurrence, and cause of death (months 1-28):

1. Develop and pilot test questionnaire (months 1-3);
2. Recruit 2250 breast cancer patients (months 4-27);
3. Conduct in-person interviews with 2,250 patients (months 4-27);
4. Conduct telephone interviews to update exposure information (month 22-28);
5. Collect paraffin-embedded blocks of breast cancer tissues from all participants (months 4-28);
6. Review medical charts to verify cancer diagnosis, conventional cancer treatments, breast cancer recurrence, and causes of death (months 4-28).

We obtained an IRB approval for the study from the Vanderbilt University in January, 2002 and from the HSRRB of the U.S. Army Medical Research and Material Command in October, 2002. We developed and pilot-tested the study questionnaire and procedures. Recruitment of study subjects began in October 2002. Up to April 30, 2004, 2483 new breast cancer patients aged between 20-74 were identified from the Shanghai Cancer Registry. Of them,

1981(80%) were recruited into the study and completed an in-person interview. Thirteen subjects died before they could be interviewed. Of the 489 non-participants, there were 278 refusals (11.2%), 136 (5.5%) who could not be located, 36(1.9%) who were out of town and 23(0.9%) not interviewed due to other reasons. The 18-months after cancer diagnosis follow-up survey were completed for 634 out of 689 patients (92%). Sixteen patients (2.3%) died before the follow-up survey, 24 subjects (3.5%) refused to participate in the follow-up survey and 5 were not interviewed due to other reasons (out of town, moving, and etc). No adverse events were reported during the study period.

Protocols for tumor tissue procurement and medical chart abstraction have been developed. We are recruiting a medical abstractor and expect to start the tumor tissue procurement and medical chart abstraction on June 15, 2004.

Key Research Accomplishments

- Developed study protocols and instruments
- Recruited and interviewed 1981 breast cancer patients;
- Completed the 18-month follow-up survey for 634 cases.

Reportable Outcomes

The study is still in progress. There are no reportable outcomes at this stage.

Conclusion

The study is progressing well as planned. To date, 1981 breast cancer survivors have been recruited into the study and the 18-month follow-up survey has been completed for 634 subjects. We have achieved the expected response rate (80%). Tumor tissue procurement and medical chart abstraction is expected to start on June 15, 2004. According to the current rate of recruitment, we will be able complete Task 1 on time.

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